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Review

Adverse events, toxicity and post-mortem data on duloxetine: Case reports and literature survey

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ABSTRACT

Duloxetine, a dual acting norepinephrine serotonin reuptake inhibitor, is a relatively new pharmacologic agent utilized in the treatment of depression, as well as diabetic neuropathic pain, fibromyalgia, and female stress urinary incontinence. This expanding scope of usage will inevitably lead to its eventual appearance during routine post-mortem toxicologic assays. Currently there is a paucity of post-mortem toxicologic data concerning duloxetine. The current report provides six additional case reports of post-mortem duloxetine levels, along with a review of duloxetine's pharmacokinetics, and the toxicologic manifestations which have been reported in the literature. The post-mortem levels reported, including the highest level recorded to date, are integrated with previously published reports to generate a foundation for a nascent guide to the interpretation of post-mortem duloxetine levels that could be encountered during routine post-mortem toxicologic analyses, and establish a basis upon which the establishment of toxic and lethal thresholds for this compound can be further elucidated with greater clarity.

1. Introduction

Duloxetine (Cymbalta®, Yentrene®, Xeristar®, Ariclaim®) is a relatively new pharmacologic agent in the ever-enlarging armamentarium of anti-depressant drugs. Duloxetine hydrochloride – [LY248686, (+)/(S)-N-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride] – is one of two main agents in the class of SNRIs (serotonin–norepinephrine reuptake inhibitor drugs). In contrast to the more familiar selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline, and citalopram, the neuropharmacology of the SNRI agents (i.e. venlafaxine and duloxetine) is one of bimodal action, blocking central synaptic reuptake of both serotonin and norepinephrine. This dual action has been shown to be more efficacious than the unimodal SSRIs in generating remission in patients with depressive disorders.[1] As a result, this compound, which is manufactured in the United States by Eli Lilly, Inc., was initially approved by the United States Food and Drug Administration (FDA) in August, 2004 for the treatment of major depressive disorder (MDD), and has since also been approved for the treatment of generalized anxiety disorder (February, 2007). In addition, anti-depressants such as duloxetine which act via serotonergic or noradrenergic mechanisms (or both) have analgesic properties that are independent of their effects on mood. This discovery provided the impetus for the implementation of clinical trials of duloxetine in the management of the symptoms of various pain conditions including peripheral neuropathic pain associated with diabetes[2] and fibromyalgia,[3] and FDA approval was obtained for those indications in September, 2004, and June, 2008, respectively. It is also marketed in the European Union under several trade names for the treatment of moderate to severe female stress urinary incontinence (Ariclaim®, Yentreve®), major depression (Xeristar®), and diabetic peripheral neuropathy (Ariclaim®, Xeristar®).

Given the expanding scope of approved indications for this drug, duloxetine continues to account for an increasing proportion of Eli Lilly's total pharmaceutical market share, with duloxetine sales of 605.1 million dollars for the first quarter of 2008, up 37% from the first quarter of 2007.[4] The recent FDA approval for its use in the treatment of fibromyalgia will undoubtedly lead to even greater dispensation of this drug to selected patient populations. As such, it would appear that there is an inevitable likelihood that duloxetine eventually will be encountered during routine post-mortem toxicologic assays. A review of the annuals reports of the American Association of Poison Control Centers (AAPCC) attests to the increasing prevalence of fatal exposures in which this drug is identified, with no reported fatal cases involving duloxetine cited before 2004, 1 case in 2004,[5] 5 cases in 2005,[6] 11 cases in 2006,[7]

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and 14 cases in 2007.[8] Unfortunately, post-mortem blood levels were documented in association with only two of those cases. At present, then, there is a paucity of published data regarding the potential post-mortem threshold blood levels for duloxetine toxicity and lethality. Indeed, aside from a recent study emanating from the Los Angeles County Coroner's Office,[9] limited data is currently available concerning the post-mortem blood levels for this drug. The aim of the current endeavor is to review the toxic manifestations reported in associated with duloxetine and provide additional case-specific data regarding levels of duloxetine encountered during routine post-mortem assays. Six additional cases are presented herein, one of which, to our knowledge, shows the highest post-mortem duloxetine level published thus far. These further contribute to the database of published duloxetine levels, and are integrated with previous data in order to create a basis upon which the establishment of toxic and lethal thresholds for this compound can be further elucidated with greater clarity.

2. Materials and methods

The Erie County Coroner's Office in Erie, PA services a population of approximately 285,000, and averages 1200 death investigations annually. Since 1992, all case investigation data has been electronically stored in a searchable database. A systematic review of that database disclosed six deaths in which duloxetine was detected, with all of these occurring from late 2006 onward. In those cases, in keeping with standard protocol, a central blood specimen was obtained and collected into commercially manufactured gray-top vacuum tubes containing sodium fluoride and potassium oxalate as preservatives. The specimen was then subject to routine toxicologic analysis, which was performed at NMS Labs, formerly National Medical Services, Willow Grove, PA, USA. Duloxetine was initially identified on the drug screen by gas chromatography–mass spectrometry (GC–MS), with extraction and quantitation through liquid chromatography and tandem mass spectrometry (LC/MS/MS). In all the cases involving duloxetine, the post-mortem interval was less than 12 h, and no signs of bodily decomposition were evident.

3. Case reports

3.1. Case 1

In October of 2006, paramedics were called to the apartment of a 57 year-old white male who was found unresponsive by his friend. He was transported to a local emergency room by ambulance and, upon arrival, was asystolic and was subsequently pronounced dead. A transdermal medication patch was located between his upper denture plate and the roof of his mouth. His past medical history included bipolar disorder and a history of drug and alcohol abuse. He had recently been released from incarceration in prison, and was also a client of a local outpatient drug rehabilitation center. According to the manager of the apartment complex, the decedent had been seen earlier that day in an intoxicated condition, and had also been known to engage in drug seeking behavior. His prescription medications, located in the apartment, included fentanyl, trazadone, duloxetine, and risperidone. Toxicologic analysis of the decedent's blood generated the following results: cocaine – 92 nanograms per milliliter (ng/mL), benzoylecgonine – 250 ng/mL, fentanyl – 26 ng/mL, norfentanyl – 3.4 ng/mL, fluoxetine – 1200 ng/mL, norfluoxetine – 1600 ng/mL, trazadone – 0.21 micrograms per milliliter (mcg/mL), duloxetine – 390 ng/mL, and ethanol – 83 milligrams per deciliter (mg/dL). The cause of death was determined to be due to combined drug and alcohol toxicity predominantly involving fentanyl. The manner of death was ruled accidental.

3.2. Case 2

The coroner's office was dispatched by the local ambulance service for an unattended residential death involving a 48 year-old white female. The decedent, who had recently complained of leg pain, dizziness, and slurred speech, had retired for a nap earlier that afternoon and was later found unresponsive by her husband. Her past medical history included obesity, asthma, and mitral valve prolapse. Prescription medications for the decedent found in the home included fentanyl, hydrocodone, gabapentin, duloxetine, lorazepam, lisinopril, theophylline, temazepam, meclizine, pantoprazole, and salsalate. The decedent had just switched physicians and was issued a prescription for transdermal fentanyl six days prior to her death. According to the prescription, one fentanyl patch was to be applied as every 72 h, and ten were dispensed in the prescription, but only four remained, when there should have been eight. The outline of the adhesive from a transdermal fentanyl patch was noted of the decedent's left shoulder, but no patch was located. The decedent's husband stated that he had applied the patch to his wife's left shoulder that morning, but it was nowhere to be found. Blood was submitted for toxicologic testing, and the following analytes were detected: hydrocodone – 45 ng/mL, fentanyl – 7.9 ng/mL, fluoxetine – 750 ng/mL, norfluoxetine – 540 ng/mL, meclizine – 19 ng/mL, duloxetine – 420 ng/mL, acetaminophen – 3.1 mcg/mL, and theophylline – 12 ng/mL. Based on the preceding toxicology results, the cause of death was opined as combined drug toxicity predominantly involving fentanyl, and the manner of death was ruled accidental.

3.3. Case 3

A 35 year-old white male was found lying supine on the floor next to a washer by his roommate at 0900. The decedent was last seen at 0500 getting ready for work. According to the family, the decedent was under medical care for chronic hip and back pain resulting from a motorcycle accident several years prior. He was taking hydrocodone for pain and duloxetine for depression in an unstructured manner. The toxicology analysis yielded acetaminophen – 1.6 mcg/mL, hydrocodone – 120 ng/mL, duloxetine – 260 ng/mL, fentanyl – 21 ng/mL. The cause of death was combined drug toxicity and the manner of death was accidental.

3.4. Case 4

The decedent, a 69 year-old white female was found clad in her nightgown, lying supine on the floor of the entrance foyer, with a quantity of blood soaked into a small mat beneath her head. There were no frank signs of visible trauma. The decedent was known to take many pills for vague symptoms and would often exhibit psychotic signs. A quantity of pills was found in the bathroom sink by police. The decedent was found to be clutching several pills which matched the pills in the sink, and several pills were present on the floor, which were identified as oxycodone. A tiny puncture–laceration was found on the crown of her head, consistent with her position, which was responsible for the blood on the bath mat. Medications found included L-thyroxine, benicar, seroquel, cymbalta, lorazepam, bupropion and oxycodone/APAP. Analysis of the blood specimen revealed acetaminophen – 98 mcg/mL, oxycodone – 600 ng/mL, diphenhydramine – 52 ng/mL, bupropion – 270 ng/mL, duloxetine – 750 ng/mL, and quetiapine – 6.4 ng/mL. The death was established as accidental resulting from a combined drug toxicity.

3.5. Case 5

A fully-clothed 45 year-old white female was found deceased on the living room sofa of her locked residence by her son, who gained entry through a window. A coroner's investigation revealed that the decedent's husband had left her several days earlier to be with another female. Family members indicated that the decedent had since threatened to commit suicide. In the early morning hours on the day of her death, the decedent telephoned her son and again threatened to commit suicide. He performed a welfare status check on her 8 h later, as noted above. On the kitchen table of the residence, there were a number of empty prescription bottles, and a hand written suicide note. The prescriptions included baclofen, gabapentin, duloxetine, and tolterodine. Analysis of the blood specimen revealed notable toxicologic findings of duloxetine – 2500 ng/mL, and baclofen – 9.0 mcg/mL. The cause of death was combined drug toxicity, and the manner of death was ruled to be suicide.

3.6. Case 6

The administrator of a local nursing home notified the coroner's office of the death of a 58 year-old white male resident of that facility, who was discovered dead in bed during early morning nursing rounds. His medical history was notable for hypertension, diabetes, peripheral vascular disease, status post remote left below-the-knee amputation, atrial fibrillation, depression, and anxiety. He had been admitted to the nursing home ten days earlier for rehabilitation following an open laparotomy, complicated by wound dehiscence and infection. The evening before his death, during the routine administration of evening medications, the decedent implied to the floor nurse that he would not "be around by tomorrow." Although he had no means to harm himself in the nursing home, the decedent had two visitors earlier that same day, and, upon his subsequent demise, the administrator was concerned that the decedent's visitors may have provided him with medication for the purpose of committing suicide. The list of prescription medications for the decedent supplied by the nursing home included lisinopril, oxycodone, duloxetine, lorazepam, pregabalin, metoprolol, simvastin, clopidogrel, and isosorbide. In light of the circumstances, an autopsy was ordered, and the post-mortem examination demonstrated the presence of severe coronary artery disease, with 99% stenosis of the circumflex coronary artery, 98% stenosis of the right coronary artery, and 80% stenosis of the left anterior descending coronary artery (LAD), along with a stent in the LAD. Patchy scarring from previous myocardial infarction was evident in the anterior and posterior papillary muscles and in the posterior interventricular septum. Hypertensive heart disease was also found, manifested by cardiomegaly (540 g), and concentric left ventricular hypertrophy (1.7 cm). Localized wound infection related to the laparotomy was also present, with chalky white fat necrosis of the abdominal pannus along the surgical incision line, and gross and microscopic findings confirming a localized abscess cavity of the anterior abdominal wall. The toxicology analysis yielded acetaminophen – 5.4 mcg/mL, duloxetine – 370 ng/mL, and meclizine – 24 ng/mL. After careful consideration of all elements of the case, the cause of death was opined to be due to hypertensive and atherosclerotic cardiovascular disease, and the manner of death was deemed natural.

4. Results

The toxicologic data from cases 1–4 revealed a variety of pharmacologic agents in each instance, many of which are psychotropic in nature and/or have central nervous system depressive actions. In addition, three had levels of fentanyl well in excess of the reported lethal threshold (case 1 = 26 ng/mL, case 2 = 7.9 ng/mL, case 3 = 21 ng/mL) while one, case 4, had an oxycodone level 600 ng/mL, well in excess of the reported lethal threshold.[10] All deaths were opined to be due to accidental combined drug toxicity, with either fentanyl or oxycodone as the predominant component associated with the fatalities. The duloxetine concentrations from these four cases were 390 ng/mL, 420 ng/mL, 260 ng/mL, and 750 ng/mL respectively.

Case 5, the suicide, showed a duloxetine level of 2500 ng/mL. Confounding this, however, was the concurrent presence of baclofen in a concentration that has been associated with a fatal outcome.[11] As such, the cause of death was deemed to be due to combined drug toxicity (duloxetine and baclofen).

Case 6 demonstrated a substantial substrate of underlying natural cardiovascular conditions, which served as the genesis for this natural death, with significant co-morbidity related to the surgical wound infection. The duloxetine level was 370 ng/mL. No causal or contributory role was ascribed to duloxetine in this case, a position that is substantiated by the absence of any corroborative and validating evidence from the scientific literature affirming the lethality of comparably low levels, which would be required to buttress such a conclusion to a reasonable degree of medical and scientific certainty. In fact, a recent nonfatal overdose case with a "benign" outcome, involving duloxetine along with trazadone, sertraline, venlafaxine, and clonazepam, has been reported, wherein the plasma duloxetine level was 384 ng/mL in a blood sample collected thirty-five (35) hours after drug ingestion.[12] This would thus support the preceding conclusion that the duloxetine level from case 6 was not a causal element in the death.

5. Discussion

Initially formulated as mixed enantiomer, known as LY227942, this agent was first reported to have potential bimodal serotonergic and noradrenergic actions from animal studies initially published in 1988.[13] It was subsequently discovered that the (+)/(S) enantiomer, LY248686, was a more potent inhibitor of serotonin reuptake,[14,15] and further animal studies suggested the potential of duloxetine as a therapeutic agent for depression.[16] Clinical trials were initiated and eventually, approval was granted by the FDA in 2004 for the treatment of depression, as noted above. Since its initial approval for depression, its utility has expanded, leading to a diversification of the medical practice areas from which dispensation of this medication transpires.

Duloxetine, as manufactured by Eli Lilly, is supplied in 20, 30, and 60 mg capsules, with the starting dosage in MDD being 40–60 mg/day, and maintenance therapy consisting of 60 mg/day. For generalized anxiety disorder, fibromyalgia, and diabetic neuropathic pain, the regimen consists of one 60 mg capsule/day. Duloxetine has an oral bioavailability ranging from 32% to 80% (mean = 50%).[17] There is a median 2 h lag until absorption begins.[18] Once ingested, the mean time until maximum blood concentration is achieved (T_{max}) has been variously reported to be between 3.5 and 6 h.[19–22] The drug is extensively bound to plasma proteins, with the reported degree of protein binding being on the order of 90–95%, predominantly due to binding with albumin and α1 acid glycoprotein.[23–25] In preclinical studies supported by the manufacturer, duloxetine's volume of distribution (V_d) has been reported to be 1640 l,[26] or approximately 20.5 L/kg for the average adult in the United States (i.e. 80 kg[27]). Compilation of data from other studies generates an average V_d of 1563 l (≈19.5 L/kg) for 118 subjects,[19–22,28] with a reported average ranging from 962 l (≈12 L/kg) for the 12 non-elderly subjects in the study by Skinner et al.,[20] up to 2909 l (≈36.4 L/kg) for the 6 healthy subjects examined by Suri

and colleagues.[19] Although blood levels increase in approximate proportionality to dosage[29] (up to 60 mg/day, see below), the pharmacologic investigations show an apparent dichotomy in the peak levels obtained. For example, in three studies, the combined average maximal plasma concentration (C_{max}) following single dose administration of 20 mg, 40 mg, or 60 mg of duloxetine was 22.9 ng/mL ($n = 16$), 46 ng/mL ($n = 24$), and 69.6 ng/mL ($n = 12$), respectively[20,21,29]; whereas average C_{max} values from two other studies for single dosage 20, 40, and 60 mg duloxetine yielded 13.7 ng/mL ($n = 22$), 27.8 ng/mL ($n = 16$), and 42.2 ng/mL ($n = 16$), respectively.[19,22] The levels obtained in the latter two studies were consistently found to be 0.6 times those of the former three studies across all single dosage regimens, although the basis for this difference is uncertain. According to the manufacturer, duloxetine has an elimination half-life ($t_{1/2}$) of about 12 h (range 8–17 h).[18] Analysis of pooled study data ($n = 114$)[19–22,28,29] yields an aggregate mean $t_{1/2}$ of 11.79 h. Metabolism occurs predominantly in the liver with biotransformation involving the cytochrome P450 system (CYP), primarily (80–90%[30]) through CYP 2D6 and 1A2 isoforms.[21] The predominant biotransformation pathways (see Fig. 1) involve oxidation of the naphthyl ring, followed by conjugation, or additional oxidation to a 5,6 catechol which is then secondarily conjugated. The N-demethylation likely occurs via CYP 2C11.[30] The formation of an epoxide compound during the metabolic breakdown of duloxetine is postulated to occur as a transient unstable chemical intermediate, which undergoes rapid conversion predominantly to dihydrodiol duloxetine through hydrolysis. Research supported by the manufacturer indicates that the epoxide intermediate was chemically unstable and is short-lived.[21] The formation of this potentially reactive epoxide intermediate is supported by the finding of some cysteine conjugates.[30] Although linear kinetics are evident throughout the recommended dosage levels, at doses beyond 60 mg bid, there is a trend toward non-linearity. Studies submitted by the sponsor to the FDA during the

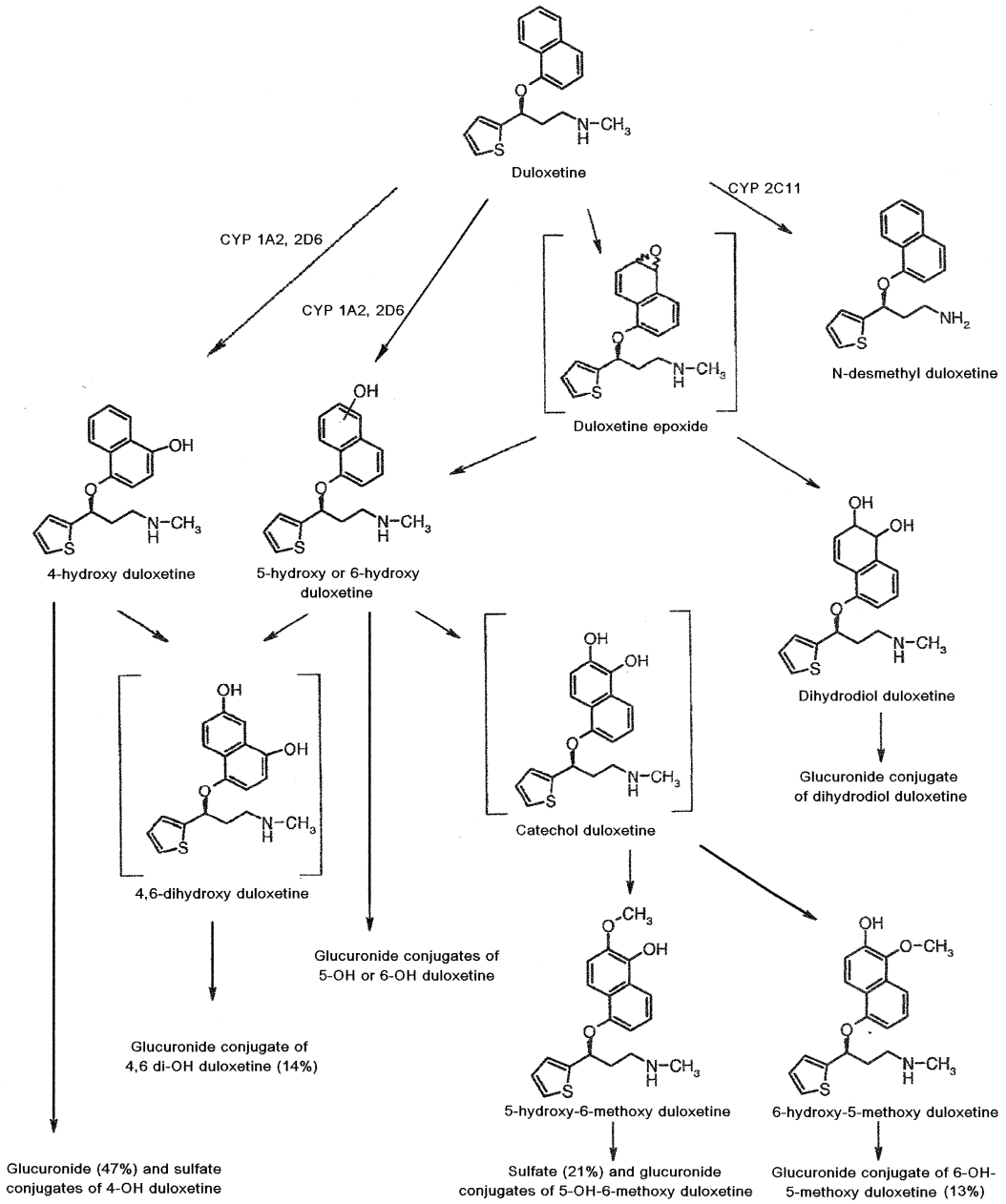

Fig. 1. Duloxetine metabolism. Compounds in brackets are postulated chemical intermediary compounds. (Adapted from Refs. [21,30].)

process of government evaluation and approval indicated that, with multiple dosing at 60 mg bid and above, the $t_{1/2}$ is increased by "several hours," AUC also increased disproportionately, and there was a reduction in clearance with no change in volume, indicating probable enzymatic saturation of CYP 2D6 with multi-dose regimens.[30] Average C_{max} levels at 60 mg bid of duloxetine are reported to be 200.6 ± 74.6 ng/mL, consistent with nonlinear kinetics.[30] Studies on the interaction between duloxetine and desipramine (a CYP 2D6 substrate) demonstrated an average increase in AUC (concentration area under the curve, ng/mL h^{-1}) of desipramine of 268%, increase in desipramine $t_{1/2}$ of 179%, and desipramine C_{max} increase of 168%.[30] As such, co-administration of medications that are predominantly metabolized by CYP 2D6 which have a narrow therapeutic index should be undertaken with caution.[31] Co-administration of duloxetine with paroxetine (a CYP 2D6 inhibitor) resulted in an average AUC increase in duloxetine of 160%, however, the paroxetine dosages used in the assessment were low (20 mg) and not at steady state, and the duloxetine doses were 40 mg per day. Consequently, with maximal paroxetine dosing under steady-state conditions, the extent of duloxetine exposure would be expected to be even larger, and would be compounded by the higher doses of duloxetine that typify clinical usage.[30] With respect to CYP 1A2, when duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP 1A2 inhibitor, to male subjects ($n = 14$), the duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold.[18] Other drugs that inhibit CYP 1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin. Some induction of CYP 2C11 may also occur.[30] Excretion occurs predominantly via the urine (72%) and feces (19%).[21]

The most commonly reported adverse reactions associated with duloxetine treatment include nausea, dry mouth, constipation, somnolence, hyperhidrosis and decreased appetite. Other adverse effects include suicidality, hepatotoxicity, orthostatic hypotension, syncope, serotonin syndrome, abnormal bleeding, especially in the setting of concomitant NSAID or aspirin use, activation of mania or hypomania, increased seizure activity, hyponatremia, and elevated blood glucose. The manufacturer advises caution when prescribing this medication in patients with hepatic or severe renal impairment, narrow-angle glaucoma, urinary retention and hesitation, and slow gastric emptying. Abrupt discontinuation of duloxetine can lead to emergence of a variety of symptoms including dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo. Duloxetine is contraindicated in those with uncontrolled narrow-angle glaucoma or with concurrent usage of monoamine oxidase inhibitors (MAOI).[18]

Adverse drug reactions (ADRs) reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in the manufacturer labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder,[31] glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Since marketing of duloxetine was initiated in the US in 2004, a number of case reports detailing duloxetine-associated ADRs have appeared in the literature. These include various dermatologic and cutaneous manifestations, including porphyria,[32] facial flushing,[33] and rash with mild anaphylatoid reaction.[34] Reports of more unique ADRs have also been published, including disabling yawning,[35] dyskinesia,[31] and gingival bleeding.[36]

Rare reports of more serious events associated with the administration of duloxetine have likewise been published. Espeleta et al.[37] discuss a case of a 32 year-old male who presented with a 2-month history of worsening fevers, chills and cough, with a chest radiograph demonstrating a peripheral upper lobe infiltrate. The patient had begun a treatment of duloxetine 4 months prior to the onset of symptoms for treatment of attention deficit hyperactivity disorder. The patient's CBC count demonstrated significant eosinophilia. At bronchoscopy, eosinophil-rich mucus was seen impacted throughout the bronchi. A transbronchial biopsy confirmed the diagnosis of eosinophilic pneumonia. With cessation of duloxetine, the symptoms, eosinophilia, and radiographic findings were reversed. This is the first reported case of eosinophilic pneumonia due to duloxetine.

It is well recognized that catecholamine level surges may be associated with myocardial dysfunction. Selective serotonin reuptake inhibitors have catecholaminergic activity but generally little cardiotoxicity. Bergman et al.[38] present a case of a 60 year-old Hispanic female who presented with a 5 day history of dizzy spells and 1 day of chest discomfort. The patient had been prescribed duloxetine that week for the treatment of diabetic neuropathy. One day after starting duloxetine, she began experiencing dyspnea, lightheadedness, and had multiple falls at home. Electrocardiography demonstrated ST-segment elevation with T-wave inversions and serum troponin I level of 3.0 ug/L (upper limit of normal, 0.059 ug/L). Coronary angiography revealed normal epicardial coronary arteries, but the left ventriculogram showed apical ballooning with basal hyperkinesis. Serum catecholamine levels were norepinephrine – 20.64 nmol/L (normal range, 0.41–4.43 nmol/L); dopamine – 1358.67 pmol/L (normal range, 0–195.84 pmol/L); epinephrine – 829.77 pmol/L (normal range, 0–600.49 pmol/L). The patient was instructed to discontinue the duloxetine and at repeat transthoracic echocardiography several weeks later, normalization of left ventricular function had occurred and a diagnosis of duloxetine-induced transient apical ballooning cardiomyopathy was rendered.

Duloxetine is contraindicated in patients with any liver disease resulting in hepatic impairment. Upon government review of premarketing studies conducted by the manufacturer, it was recommended that a descriptive precautionary statement be included in the package insert. As such, the initial product labeling associated with release of duloxetine in August 2004 included provisions primarily aimed at its effect on liver function tests. In placebo-controlled trials in patients with major depressive disorder, increases of alanine transaminase (ALT) levels to greater than 3 times the upper limit of normal occurred in 0.9% of duloxetine-treated patients. In patients with diabetic peripheral neuropathy, increases of ALT levels to greater than three times the upper limit of normal occurred in 1.68% of duloxetine-treated patients. In the full cohort of placebo-controlled trials, there was evidence of a dose–response relationship for ALT level increases greater than 3 times the upper limit of normal. The median time to detection of the laboratory abnormalities was 2 months.[39] In addition, a pharmacokinetic study showed that single non-therapeutic dose of 20 mg duloxetine in six cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance that was only approximately 15% that of age- and gender-matched healthy subjects, with a 3.5-fold increase in AUC, and a half-life approximately 3.5-times longer.[19]

Post marketing reports of hepatotoxicity associated with duloxetine have been reported. Included among these is a report by Hanje, et al.[40] who published a case of fulminant hepatic failure involving duloxetine. The patient, a 56 year-old woman with a history of non-Hodgkin's lymphoma and depression, was admitted to the hospital with jaundice and fatigue. Diagnosed with lymphoma in 1997, the patient had undergone chemotherapy for 1 year and

was considered in complete remission. She had been treated with duloxetine and maintained on 30 mg/day for approximately 1 year. Approximately 6 weeks before presentation, her duloxetine dose was increased to 60 mg/day and she was prescribed 15 mg/night of mitrazapine for insomnia. 4 weeks after increasing the duloxetine and adding the mitrazapine to her daily regimen, she began to complain of generalized fatigue. A week after that she began to complain of right upper quadrant pain, and then she noticed herself to be jaundiced for the first time. The patient was then hospitalized for 3 days, where evaluation disclosed a total bilirubin level of 9.9 mg/dL, conjugated bilirubin level of 6.8 mg/dL, alkaline phosphatase level of 307 u/L, aspartate transaminase level (AST) of 2477 u/L, ALT level of 2777 u/L, albumin of 3.3 g/dL, and serum protein level of 7.4 g/dL. Her duloxetine was discontinued on admission. Computed tomography (CT) of her abdomen and pelvis without intravenous contrast revealed a nodular liver contour with an enlarged portal vein and borderline splenomegaly (12 cm). An outpatient endoscopic retrograde cholangiopancreatography found no evidence of obstruction or ductal dilation. She presented to the hospital again 48 h later with new onset of altered mental status. Her total bilirubin level at that time was 18.8 mg/dL, AST level was 1644 u/L, ALT level was 783 u/L, and her international normalized ration was 2.8. Over the next 3 days, her liver function test (LFT) results continued to worsen and her mental status deteriorated. Patient was believed to be in fulminant hepatic failure, required intubation, was listed for emergent liver transplantation, and transferred to a tertiary care transplant center. Serum and urine toxicology was negative. Liver serology, quantitative hepatitis C polymerase chain reaction, antinuclear antibody, antimitochondrial antibody, anti-smooth muscle antibody, and antineutrophilic cytoplasmic antibody tests were all negative. Ceruloplasmin, ferritin, and alpha-1 antitrypsin levels were within normal limits. Blood and urine culture results were negative. The patient was diagnosed with severe nonspecific encephalopathy and was treated with lactulose and subsequently given both fresh-frozen plasma and recombinant factor VIIa with placement of an intracranial pressure monitor. Despite continuous supportive care, the patient's clinical condition deteriorated over the next 48 h. The patient was deemed too critical to undergo transplantation and was removed from the transplant list. After extensive consultation with the family, the decision was made to withdraw care. A formal autopsy was refused; however, a percutaneous liver biopsy specimen was obtained. This showed a mixed inflammatory infiltrate within the portal and lobular areas consisting mainly of neutrophils with occasional eosinophils and lymphocytes. Moderate micro- and macro-vesicular steatosis and hepatocellular cholestasis were seen. There was ballooning degeneration of hepatocytes with bridging necrosis and centrilobular hepatocyte dropout. The portal areas showed bile ductular proliferation. Trichrome, reticulin, and elastic stains suggested bridging necrosis and edema rather than cirrhosis. Focal portal and perisinusoidal fibrosis were seen. Although nonspecific, these histologic changes were consistent with subacute liver injury. With the presence of focal fibrosis, chronic underlying liver disease could not be excluded. The authors indicate that the patient's clinical course and the temporal relationship between the increase in her duloxetine dose and the onset of symptoms argue in favor of severe drug-induced liver injury. The patient was maintained on a lower dose of duloxetine for almost a year without apparent difficulties, developing clinically significant hepatotoxicity only after the dose was doubled. This also is consistent with earlier trials showing a dose-dependent nature of hepatic injury with duloxetine use. Causality was estimated using the Naranjo nomogram,[41] the Council for International Organizations of Medical Sciences scale,[42] and the Maria and Victorino clinical scale[43] indicating a probable association between the increase in duloxetine dose and the patient's hepatic injury. The fact that her clinical course continued to worsen after removal of the drug is not surprising given the severity of her condition on presentation and the likelihood that she had continued taking the medications for weeks after the initial onset of symptoms. Although her duloxetine dose was increased at the same time she began taking mirtazapine, mirtazapine has rarely been associated with clinically significant increases in serum transaminase levels in almost 10 years of postmarketing surveillance and is not thought to have a narrow therapeutic index. No laboratory data were available to determine whether the patient had pre-existing increases in her LFTs, either before or during the time she was on the lower dose of duloxetine. The patient carried no prior diagnosis of chronic liver disease. Although the abdominal CT demonstrated a nodular liver, suggesting underlying cirrhosis, the patient's biopsy examination showed only minimal fibrosis without cirrhosis and the degree of necrosis and parenchymal collapse alternatively could explain the appearance of a nodular liver on CT. Thus, it seems unlikely the patient had significant underlying chronic liver disease however, given the lack of laboratory data, this possibility could not be excluded, but nonetheless seems remote.

In response to reports such as this, in October of 2005, the Eli Lilly Company and the FDA notified healthcare professionals of revision to the Precautions – Hepatotoxicity section of the prescribing information for duloxetine.[44] The FDA indicated that the "postmarketing reports of hepatic injury (including hepatitis and cholestatic jaundice) suggest that patients with pre-existing liver disease who take duloxetine may have an increased risk for further liver damage. The new labeling extends the Precaution against using Cymbalta in patients with substantial alcohol use to include those patients with chronic liver disease. It is recommended that Cymbalta not be administered to patients with any hepatic insufficiency."[45]

Nonetheless, the FDA announced a second label change in June, 2008, which took effect on August 11, 2008. The new labeling involved a revision of the Warnings and Precautions section, Hepatotoxicity subsection. The added content now begins with, "There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury."[46]

Likely owing in part to its relatively recent introduction into the market, detailed reports in the literature of intentional or accidental misuse of duloxetine causing untoward toxic manifestations and/or death have been sparse. Menchetti et al.[12] recently reported a case of an intentional overdose by a 66 year-old white female involving 540 mg of duloxetine, along with trazadone (675 mg), venlafaxine, sertraline, and clonazepam. She was found by her housekeeper in a confused state approximately 5 h after the ingestion, and was admitted to the hospital in a somnolent, disoriented, confused condition. She underwent gastric lavage with water, charcoal and magnesium sulfate. Although cardiovascular changes included hypotension, sinus bradycardia and "possibly a slightly prolonged QTc interval" on ECG, she was transferred to the inpatient psychiatric ward 4 h after presentation to the hospital, at which time she was lucid, cooperative, and oriented, and her subsequent course and recovery were uneventful. Further overdose cases were encountered during premarketing clinical trials, where four cases of overdose were reported. The minimum ingestion of duloxetine was 300 mg while the highest reported ingestion was approximately 1400 mg.[31] All patients survived the overdose event.

Starting in 2004, The AAPCC Toxic Exposure Surveillance System (TESS) has reported 17 deaths in which duloxetine was

detected.[5–8] Post-mortem blood levels were documented in association with two of those cases. No fatalities with duloxetine were recorded prior to 2004. Of the 31 deaths, 27 were classified as definite or suspected suicides. In six instances, four of which were suicides, duloxetine was determined to be the primary pharmacologic agent responsible for the fatality. In the fifth case, the reason for the fatal ingestion was classified as "unintentional unknown," defined as an exposure determined to be unintentional, but the exact reason is unknown. The remaining death in which duloxetine was listed as the primary agent was the ADR reported by Hanje described above. Deaths with duloxetine from the AAPCC TESS database are categorized in Table 1. For each case, the first agent listed was deemed most responsible for the death, as per the AAPCC TESS protocol whereby assignment was by agreement of the medical director of the reporting center and at least 2 additional toxicologist reviewers. Additional agents implicated (up to a maximum of 3 total agents in cases prior to 2006) are listed below the primary agent.

A series of 12 fatalities in which duloxetine was detected on post-mortem toxicologic analysis was recently reported from the Los Angeles County Coroner's Office.[9] In all instances, the analysis was performed using a central blood specimen. Three cases were non-drug related fatalities (diabetic ketoacidosis, drowning, and atherosclerotic cardiovascular disease). In three other cases, the deaths were ascribed to a single drug (fentanyl, morphine and methadone), with duloxetine playing no role in the fatal outcome. Four cases involved accidental or unintentional multiple drug toxicity, with no less than 5 pharmacologic agents (including duloxetine) found in any case. The remaining case was a suicide with trazadone, venlafaxine, and duloxetine. However, a comparison between the prescription information, remaining pills from the bottle, and the dosing records indicated that this individual was in compliance with the duloxetine dosing regimen in this case. Moreover, the trazadone level (16.0 mg/L) was in excess of the lethal threshold reported for this agent, and the venlafaxine level (6.8 mg/L) was also above the threshold level associated with a fatal outcome.[47] The average and range of post-mortem central blood duloxetine values associated with the 12 cases was 237.5 ng/mL, and ND – 590 ng/mL, respectively. The authors indicated that duloxetine was not implicated as the sole cause of death in any of the reported cases. In addition to the suicide, it was concluded that sufficient evidence of dosing compliance was manifest in five others, suggesting that the duloxetine blood levels in those six cases could be taken to be potentially representative of post-mortem therapeutic values. The specific blood levels from those cases were ND,[1] 50, 280, 300, 220 and 220. The average blood level from those six cases was 183.16 ng/mL (range: ND* – 300 ng/mL).

A data compilation of all cases reported from the AAPCC TESS reports, the L.A. County Coroner's Office and the cases reported herein was undertaken to determine the frequency of concurrence of other specific drugs with duloxetine in the drug fatalities associated with non-natural deaths (i.e. accidental, unintentional, or suicidal ingestions). Thus, deaths from natural causes and those unrelated to drug intake have been excluded from this analysis. Likewise, the ADR from the AAPCC TESS cases has also been omitted. 44 cases remained for evaluation. Among prescription medications, the drug that was found to be present most frequently along with duloxetine was trazodone, which was found along with duloxetine in 9 of the 44 cases ($n = 9$). Other individual drugs found to be concurrently present along with duloxetine in more than 1 instance were lamotrigine, diphenhydramine and quetiapine ($n = 8$); bupropion, and hydrocodone ($n = 7$); methadone ($n = 6$); clonazepam, ethanol and fluoxetine ($n = 5$); citalopram/escitalopram, fentanyl, lorazepam, and oxycodone ($n = 4$); alprazolam, cyclobenzaprine, hydroxyzine, levothyroxine, morphine, tramadol, venlafaxine and ziprasidone ($n = 3$); and amitriptyline, amlodipine, atenolol, baclofen, benzodiazepine (not otherwise specified), codeine, flurazepam, gabapentin, meclizine, meprobamate, nortriptyline, promethazine, risperidone, thyroid preparation (not otherwise specified), valproic acid, and zolpidem ($n = 2$). Whether the frequent concurrent presence of some of these agents in association with duloxetine is merely representative of an epiphenomenon or has implications relative to drug–drug interactions specific to duloxetine is unclear, as the low number of cases precludes the extrapolation of any conclusions based on this limited data alone, although it is interesting to note that trazadone was also concurrently involved in the case report of Menchetti et al., as noted above.

At present, owing largely to its relatively recent introduction into the market, there is paucity of post-mortem data regarding the potentially toxic and lethal concentrations of duloxetine. In an effort to provide some insight into this matter, integration of the data from the current cases reported herein, those previously reported from the L.A. County Coroner's Office, and the two cases with post-mortem duloxetine levels from the AAPCC TESS reports demonstrates some potential trends in the duloxetine data. Stratification of these cases was undertaken, whereby they were grouped into two categories of deaths: (1) those considered to be compliant with the duloxetine prescription regimen and representative of post-mortem therapeutic levels[9] and (2) non-compliant decedents with combined drug toxicity involving duloxetine, either accidental or suicidal. This data is presented in Table 2. It should be noted that, for the purpose of this derivation, only central post-mortem blood specimens were used in the compilation of the results in order to facilitate a uniform analysis. The average duloxetine toxicity level identified in the group that was compliant with their regimen was established as 183.16 ng/mL. In the duloxetine non-compliant combined drug toxicity (accidental or suicidal) group, the average duloxetine level was 698.75 ng/mL. The mean duloxetine levels for those cases with fatal drug toxicity involving duloxetine was nearly 4-times higher than those whose deaths were representative of therapeutic levels. This data was subject to statistical analysis using the Mann–Whitney U test, a non-parametric test for assessing whether two independent samples of observations come from the same distribution. This statistical application, yielded a p value < 0.05, indicating a degree of statistical significance between these two groups. As such, the data from Table 2 may provide a nascent preliminary guide to the interpretation of post-mortem duloxetine levels that could be encountered during routine post-mortem toxicologic analyses. The data suggest that, at levels greater than 700 ng/mL, duloxetine may, under certain circumstances, potentially act in a contributory manner in the lethal pharmacodynamic substrate to precipitate a fatal outcome. Nonetheless, without and until the publication of additional data, it is not yet possible to arrive at a set of threshold post-mortem duloxetine levels that are associated with definitive toxicity or lethality.

To this end, further discussion of case 5, where the post-mortem duloxetine level was 2500 ng/mL, is warranted. This case is, by far, the highest post-mortem blood duloxetine level reported in the literature thus far. The duloxetine prescription was for one 60-mg capsule per day, with 30 pills dispensed, and was filled 27 days prior to the date of death and also the date last confirmed to be alive. If the duloxetine prescribing regimen had been followed, then only 3 duloxetine capsules (i.e. 180 mg) would have remained

[1] Duloxetine was initially qualitatively detected on routine drug screening using GC–NPD (gas chromatography with nitrogen–phosphorous detection) and GC–MS (GC–mass spectrophotometry). With positive screening, quantitation was undertaken using GCMS with a limit of detection at 30 ng/ml. The "ND" case was detected using the qualitative screening method, but fell below the quantitative threshold of 30 ng/ml, and is assigned the most statistically conservative value possible at 29 ng/ml.

Table 1
AAPCC TESS fatalities with duloxetine.

Age (in years)	MOD	Substances		Blood levels (when available)
40+	S	Duloxetine (Dul) Hydroxyzine (Hyd) Cetirizine (Cert)		Dul = 380 ng/mL Hyd = 320 ng/mL Cert = 740 ng/mL
42	S	Duloxetine Metaxalone	Methadone Oxcarbazepine	
44	S	Duloxetine Bupropion Ethanol Thyroid preparation Trazodone Lamotrigine	Ziprasidone Cyproheptadine Buspirone Chlorpromazine Penicillin Chlordiazepoxide Hydroxyzine	
42	S	Duloxetine Bupropion Clonazepam		
56	A[a]	Duloxetine		
53	Un Unk[b]	Duloxetine Risperidone Lamotrigine	Clonazepam Zolpidem	
20	S	Ziprasidone Duloxetine		
65	S	Acetaminophen (Ac) Aspirin (ASA) Duloxetine Methocarbamol		Ac = 146.5 mcg/mL ASA = 45.1 mg/dL
26	S	Ac Valproic acid (Va) Vitamins/iron Duloxetine Fosinopril		Ac = 141 mg/L Va = 125 mcg/mL Iron = 418 mcg/mL
39	S	Ac/opioid, nos Tramadol Carisoprodol Fexofenadine Naproxen Thyroid preparation	Quetiapina Trazodone Duloxetine Clonazepam Ethanol	Ac = 86 mcg/mL
57	S	Ac/diphenhydramine Levothyroxine	Clonazepam Duloxetine	Ac = 500 mcg/mL
98	S	Amlodipine Duloxetine Levothyroxine		
>19	S	Nifedipine Duloxetine Sertraline Others – not specified		
44	S	Lamotrigine Quetiapine Duloxetine Lorazepam	Modafinil Vardenafil Thorazine Tramadol	
31	S	Methadone Ac/oxycodone Hydrocodone Cyclobenzaprine	Eszopiclone Duloxetine Risperidone	
39	S	Amitriptyline (Am) Bupropion (Bu) Duloxetine (Dul)		Am = 1.04 mg/L Bu = 1.15 mg/L Dul = 0.69 mg/L
58	S	Atenolol Duloxetine		
31	S	Venlafaxine Valpoic acid (Va) Hydrocodone Codeine/ Promethazine	Trazodone Pseudoephedrine Diphenhydramine Duloxetine Ac	Va = 232 mcg/mL Ac = 134 mcg/mL
40	S	Atenolol Amlodipine Trazodone	Escitalopram Duloxetine Losartan	
47	S	Verapamil (Ver)	Ver = 11.4 mcg/mL	

Table 1 (*continued*)

Age (in years)	MOD	Substances		Blood levels (when available)
		Duloxetine Cyclobenzaprine Others – not specified		
24	S	Bupropion Quetiapine Duloxetine Lamotrigine		
28	S	Diltiazem Bupropion Quetiapine Clonidine	Tizanidine Duloxetine Ziprasidone Gabapentin	
50	S	Tricyclic anti-depressants, nos Clozapine Duloxetine Lamotrigine		
54	S	Doxepine Citalopram Trazodone Flurazepam Acetaminophen	Duloxetin Fluoxetine Montelukast Fenofibrate	
56	S	Quetiapine Carbamazepine Duloxetine	Lamotrigine Lorazepam Ibuprofen	
37	S	Bupropion Quetiapine Baclofen Promethazine Methadone Duloxetine Clonazepam	Zolpidem Lithium Levothyroxine Lamotrigine Efavirenz Emtricitabine/ Tenofovir	
44	S	Nortriptyline (Nor) Metformin (Metf) Glipizide Lisinopril Duloxetine		Nor = 760 ng/mL Metf = 12 mcg/mL
53	S	Oxycodone Duloxetine Trazodone Alprazolam Skeletal muscle relaxants, NOS		
58	S	Lorazepam Duloxetine Benzodiazepine Alprazolam		
25	S	Olanzapine Lamotrigine Duloxetine		
31	Unt-T	Unknown Ddrug Duloxetine Fluoxetine	Benzodiazepine Ciprofloxacin	

Abbreviations: MOD – manner of death, S – suicide, A – accidental, Un Unk – unintentional unknown (see text), Unt-T – unintentional therapeutic error, NOS – not otherwise specified.

[a] Case reported by Hanje, see text.

[b] See text for discussion.

Table 2
Duloxetine levels with bimodal stratification.

Duloxetine level (ng/mL)	Duloxetine case type		Mann–Whitney *p* value
	Dosage compliant, *n* = 6	Combined drug toxicity (accidental or suicidal), non-compliant, *n* = 8	
Mean (range)	183.16 (n.d.[a] – 300)	698.75 (170–2500)	<0.05

[a] n.d. = not detected, assigned a value of 29 ng/mL (see discussion).

in the bottle and been available at the time of the fatal ingestion. The bottle was empty when the decedent was discovered. If the average dose proportionality constant of 0.95 ng/mL/mg derived by Sharma[28] is applied, then the total duloxetine ingestion would have amounted to 2632 mg. With a known dose strength of 60 mg per capsule, the calculated ingested number of capsules required to achieve this is approximately 44, which exceeds the number of available capsules by 41 if there was compliance with

the dosing regimen, and also exceeds the total number of capsules initially dispensed with the prescription (i.e. 30 capsules) by 14 (and which would also mandate that no therapeutic ingestion had *ever* occurred from the time the prescription was filled until the time of the lethal suicidal ingestion). This profound disparity has a number of potential explanations, none of which are necessarily exclusive of one-another. First, the proposed dose proportionality constant cited above was provided as an average, but the actual range was quite wide, ranging from 0.38 to 1.89 ng/mL/mg. If the lowest value is applied for this case, the total duloxetine ingestion required to obtain a blood level of 2500 ng/mL is 6579 mg, but if the highest value is applied, the total duloxetine ingestion becomes 1322 mg, or 22 tablets, which is potentially feasible. However, the application of the average dose proportionality constant derived by Sharma, which was extrapolated from a study of only eight subjects and utilized doses of only 20, 30, and 40 mg bid, may not be suitable for application outside the parameters of the study from which it was generated, and therefore may not be appropriate in this case. Although application of the highest value leads to a more congruent situation, nonetheless, the range published may not be truly representative of duloxetine dose proportionality in a larger population, or in cases with higher doses. Following from this, the application of such a dose proportionality constant is reliant on linear kinetics, which may not be valid at more extreme dose ranges, where the emergence of non-linearity evinces the presence of potential saturable processes. Indeed, the studies submitted by the drug sponsor to the FDA during the process of government evaluation and approval indicated that, at doses above 60-mg bid, there was probable enzymatic saturation of CYP 2D6, with duloxetine blood levels consistent with nonlinear kinetics.[30] As such, in cases with high blood levels, the proposed dose proportionality constant may not be operative. In addition, consideration of potential post-mortem redistribution (PMR), a pervasive issue in the interpretation of autopsy blood toxicology values, is warranted. This phenomenon, which has been previously reviewed elsewhere,[48] tends to be most pronounced with drugs that are highly protein bound and with those that have a high V_d. Duloxetine has both of these characteristics, and therefore may undergo extensive PMR. The average central-to-femoral blood duloxetine ratio obtained by Anderson et al., was 1.98 (1.15–3.13; $n = 7$), indicative of a moderately high degree of PMR, approaching those associated with the tricyclic anti-depressants. Similarly, caution is required whenever any attempt to compare antemortem blood values to post-mortem values is undertaken, as marked differences in drug levels can occur. In a study by Cook et al.,[49] the variation between antemortem and post-mortem drug levels was found to be as high as 11-fold, with drugs exhibiting PMR having a tendency to also have high post-mortem-to-antemortem ratios. Indeed, those authors issued the strongly-worded caveat, "that it can be dangerous to attempt to relate a drug concentration found at post-mortem examination to the antemortem circulating concentration or to the antemortem dose received." Closer examination of Anderson's data reaffirms this, for in six cases where duloxetine dosage compliance was validated, with an average calculated dosage of 55 mg of duloxetine per day, the average post-mortem level was 178.3 ng/mL, whereas antemortem dosage studies of 60-mg duloxetine per day yielded average maximum concentrations ranging between 42.2 ng/mL ($n = 16$)[19,22] and 69.6 ng/mL ($n = 12$),[20,21,29] indicating the possibility of a post-mortem-to-antemortem ratio of as high as 4.2:1 for duloxetine.

Nonetheless, irrespective of the influence of the preceding factors upon the antemortem pharmacokinetics and agonal pharmacodynamics, the level found in the central blood from case 5 (i.e. 2500 ng/mL) remains more than 14-times higher than the average of those obtained from post-mortem central blood specimens in individuals known to be compliant in their duloxetine prescription regimens (i.e. 183.16 ng/mL), and approximately 3.6 times higher than the maximal post-mortem level reported.[8] Although the case was one of obvious suicidal intent, the difficulty in interpretation with respect to the potential significance of the duloxetine level arises from the concurrent presence of baclofen in the post-mortem blood specimen, at a concentration of 9.0 mcg/mL. A gamma-aminobutyric acid analogue, baclofen is typically utilized in the management of muscle spasticity, as frequently seen in multiple sclerosis. Intentional or accidental overdose with baclofen is productive of toxic manifestations including drowsiness, confusion, somnolence, hypotonia, seizures, respiratory depression, bradycardia and coma.[50–52] Fatalities have been reported with post-mortem blood level as low as 6.0 mcg/mL,[11] whereas levels in nonfatal oral overdoses have been as high as 15 mcg/mL,[50] indicating some potential overlap between the toxic and lethal ranges. The literature is generally supportive of, at the least, toxic manifestations associated with baclofen levels comparable to that seen in case 3. However, in the absence of more definitive and conclusive post-mortem data on duloxetine, it would be inappropriate to conclude that, in the absence of the baclofen, a fatal outcome from duloxetine would have transpired. On the other hand, there is a clear possibility that in this particular case, in the absence of duloxetine, a fatal outcome from the baclofen alone may have transpired. Nonetheless, since survival has been documented at baclofen levels comparable to that seen here, it would be entirely inappropriate to simply dismiss the potential role of duloxetine as an exacerbating factor for this demise, particularly in light of the extraordinarily high level. A conservative determination was therefore made to rule the death as being due to combined drug toxicity. Although it is compelling to speculate that the extreme duloxetine level alone may have been sufficient to cause the death in this instance, the presence of baclofen undermines the credibility of any such assertion. Only with the addition of future cases added to those currently published will a more definitive algorithm emerge regarding threshold post-mortem blood levels for lethality and toxicity for duloxetine. It is hoped and encouraged that further published reports detailing post-mortem duloxetine levels, and in particular those fatal cases involving *only* duloxetine, will be forthcoming, which will provide much needed clarification on this recent and evolving issue.

Conflict of interest

There is no conflict of interest.

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None declared.

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